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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,128	09/14/2000	Shuji Miyagawa	197330US0	9580

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/662,128	MIYAGAWA ET AL.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-24 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 13 is acknowledged. The traversal is on the ground(s) that the claims of Groups II-V are dependent on the claims of Group I, and Groups II and III are drawn to the use of the invention of Group I, a Cre recombinase gene. Applicants further argues that there is no search burden for the entire application because Groups II-V have same classification.

This is not found persuasive because of the following reasons. The inventions of Groups I-V are patentably distinct for the same reasons of the record as set forth in the Office Action mailed on 2/6/02. A search of the subject matter of one invention would not be co-extensive with a search of the other invention, and therefore the search would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 12-21 and newly added claims 22-24 are withdrawn from consideration as being directed to non-elected subject matter. Claims 1-11 are currently under examination.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 8 is rejected under 35 U.S.C. 101 because it is not directed to statutory subject matter. It is PTO policy not to issue claims that encompass humans (see 1077 OG 24, April 21, 1987). This rejection may be overcome by inserting "non-human" before "animal".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a transgenic animal comprising a polynucleotide encoding a modified Cre recombinase. The specification discloses a vector comprising a polynucleotide encoding a modified Cre recombinase. However, the specification fails to provide an enabling disclosure for a transgenic animal exhibiting any phenotype as a consequence of expression of a modified Cre recombinase. The claim encompasses transgenic animals having any phenotype, but the specification only teaches how to use the animals expressing said Cre recominase. In the absence of specific guidance, one skilled in the art would not know how to use an transgenic animal without any phenotype and undue experimentation would have been required to determine how to use the claimed animals in the absence of a disclosed phenotype. The phenotype of the transgenic animal is a critical feature of the invention. However, the phenotype of the transgenic animal is unpredictable for a number of reasons as discussed below.

The specification fails to provide an enabling disclosure for any transgenic animal of the type claimed. The specification teaches only how to use transgenic animal having the desired transgene-dependent phenotypic alteration. The mere capability to perform gene transfer in a given species is not enabling for the claimed transgenic animal because desired phenotype cannot be predictably achieved simply because the animal having the desired genotype. While gene transfer techniques are well developed for a number of species, especially mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection of retrovirus-mediated gene transfer. However, the state of art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p.61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic mouse. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic mouse depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, constructs that use heterologous genetic elements will not always confer the desired phenotype in a mouse. This is especially relevant for the use of genetic elements from species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic mice. Even differences in the genetic background of

transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). Thus, in the absence of specific guidance, the production of a transgene-dependent phenotypic alteration resulting from introducing a modified Cre recombinase into an animal is unpredictable. In the absence of specific guidance, one skilled in the art would not know how to use a transgenic animal that does not exhibit he specific transgene-dependent phenotype disclosed in the instant specification, without undue experimentation. In view of the limited guidance in the specification and unpredictability in the art, one skilled in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic animal.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 5, the term "location-specific promoter" renders the claims indefinite because it is unclear what kind of promoter applicants are referring to. The specification fails to provide a definition for this term. It is unclear whether the promoter is inducible depending on tissue specificity, location of the body of the animal, or geographic location of said animal. Applicant should use terms consistent with what is acceptable in the relevant art.

Regarding claim 6, the term "time-specific promoter" renders the claims indefinite because it is unclear what kind of promoter applicants are referring to. It is unclear whether the promoter is inducible at a particular time of a day or depending on the length of the time after the

vector is introduced into an animal. The specification fails to provide a definition for this term. Applicants should use terms consistent with what is acceptable in the relevant art.

Claim 7 recites the limitation "polynucleotide" in line 1. However, claim 1 (which claim 7 depends on) does not recite any "polynucleotide." There is insufficient antecedent basis for this limitation in the claim.

Regarding claims 8-11, the phrase "gene encoding the polynucleotide" renders the claims indefinite because "gene" encodes polypeptide or protein but not "polynucleotide." It is unclear the nature of the gene that is claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over St-Onge et al (1996, Nucleic Acid Research, Vol 24, No. 19, 3875-3877) and Bergemann et al. (1995, Nucleic Acid Research, Vol 23, No. 21, 4451-4456), in view of Zhang et al (1996, Biochemical and Biophysical Research Communications, Vol 227, 707-711) and Nakamura et al (1998, Nucleic Acid Research, Vol 26, No. 1, 334).

The claims are drawn to a nucleic acid (and complementary sequence to the nucleic acid) encoding Cre recombinase from bacterial-phage original, wherein the codons are modified for optimized expression in mammalian cells. The claims are further drawn to said nucleic acid further comprising a inducible promoter, a marker gene, a nucleic acid encoding a nuclear transport signal or a Kozak sequence.

St-Onge et al. teach a transgenic mouse comprising a Cre recombinase gene under the control of CMV promoter fused to seven copies of tetO sequences (see page 3875, 1st column, lines 7-9). St-Onge et al. further teach that the Cre recombinase expression can be suppressed by administering tetracycline to said mouse (see page Figure 3A, and page 3876, bridging paragraph of col.1 and col.2). St-Onge et al. also teach that a mutant tetR/VP16 that transactivates the tetO-promoter in the presence of tetracycline (see page 3877, line 1). However, St-Onge et al. do not teach a nucleic acid encoding a modified Cre recombinase under the control of an inducible promoter.

Bergemann et al. teach a vector pJBCre31 that comprising a Cre recombinase gene, an N-terminal Kozak sequence, a nuclear transport signal, and a 9E10 epitope for immunological detection (see page 4452, col.1, 2nd paragraph). However, Bergemann et al. do not teach a vector comprising a modified Cre recombinase gene.

Nakamura et al. teach codon usage tabulated from the international DNA sequence database and further provided the URL link of a web site contain such information (see entire document).

Zhang et al. teach that changing codons encoding a jelly fish green fluorescent protein to mammalian codon resulted in higher expression of the protein. Zhang et al. teach that a EGFP that is codon-optimized by using the favored codons of highly expressed human proteins in place of the jelly fish codons increases expression in mammalian cells (see page 708, 3rd paragraph, lines 7-9).

It would have been obvious to one of ordinary skill of art to modify the codons of Cre recombinase from bacterial phage to mammalian codons. The ordinary artisan would have been motivated to do so to increase the expression of Cre recombinase in mammalian cells as taught by Zhang et al. The ordinary artisan would have reasonable expectation of success because codon usage profiles have been generated for proteins of different origin (as taught by Nakamura et al), and replacement of such codons results in increased expression of GFP (as taught by Zhang et al). Thus, replacing the codons of Cre recombinase from bacterial phage origin, as taught by St-Onge et al. and Bergemann et al., to codons optimized for mammalian expression (information that can be obtained from the web site taught by Nakamura et al.) would have been obvious to one of ordinary skill in the art at the time of the invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
May 20, 2002

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